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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,340	03/23/2001	Bert Vogelstein	01107.00074	4414

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 08/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,340	VOGELSTEIN ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-18 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-18 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 10-15 have been amended. Claims 10-18 and 23 are pending and under consideration.

2. Sections of the text of Title 35 U.S. Code not found in this action can be found in a previous action.

3. Claims 10-18 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.. Claim 10 has been amended to delete the limitation of "screening compounds to identify anti-cancer agents", thus the newly amended claim is broader in scope than the original claim 10. Further, the specification as filed states that an "embodiment of the invention is a method of screening compounds to identify anti-cancer agents" (page 4, lines 20-21) but does not identify any other screening methods to identify agents outside of the realm of anticancer agents. One of skill in the art would reasonable conclude that applicant was not in possession of the broadly claimed invention.

4. Claims 11-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

Claim 10 is drawn to a method of screening compounds comprising contacting a test compound with two isogenic mammalian cell lines, wherein the first cell line is securing proficient and the second cell line is securin defective and determining if said compound preferentially inhibits the growth of the first cell line relative to the second cell line preferentially inhibits growth of the first cell line relative to the second cell line. Claim 11-15 embody the method of claim 10 wherein a test compound is identified which inhibits the growth of the first

cell line at least 2-fold, 5-fild, 10-fold, 20-fold and 50-fold more than the second cell line, respectively..

To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provide an enabling disclosure of how to make and use a claimed invention. The specification does not teach a particular test agent which would inhibit the growth of the first cell line relative to the second cell line and specifically does not teach how to select test agents which will inhibit the growth of the first cell line relative to the second cell line by at least 2, 5, 10 or 20 fold over that of the second cell line. The specification does not teach any structural or biochemical requirements which should be present in the genus of test compounds which would allow one of skill in the art to select a set of test compounds and subject them to the instant method with a reasonable expectation of success of identifying an agent which would inhibit the growth of the first cell line relative to the second cell line at the claimed levels. Further, the specification does not teach a partial structure coupled with a biochemical characteristic which would provide a reasonable expectation of success to one of skill in the art for the selection of test agents which would inhibit the cell lines as claimed. Given the lack of guidance in the specification for how to find a test agent which would function as claimed, one of skill in the art would be subject to undue experimentation in order to carry out the claimed methods.

5. Claim 10, 16, 18 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Melmed et al (WO 98/22587) as evidenced by Morales et al (Oncogene, 2000, vol. 19, pp. 403-409, cited in a previous action) in view of Lengauer et al (Nature, 1998, Vol. 396, pp. 643-649, cited in a previous action).

Claim 10 is drawn to a method of screening compounds comprising contacting a test compound with two isogenic mammalian cell lines, wherein the first cell line is securing proficient and the second cell line is securin defective and determining if said compound preferentially inhibits the growth of the first cell line relative to the second cell line preferentially inhibits growth of the first cell line relative to the second cell line. Claim 16 embodies the method of claim 10 wherein the cells are in culture when contacted with the test agent. Claim 18 embodies the method of claim 10 wherein the test compound preferentially kills the first cell line relative to the second cell line.

Morales teach that PTTG is synonymous with securin.

Melmed et al teach human PTTG (page 5, line 16) and that wild-type PTTG unexpectedly inhibits proliferation in cultured transfected cells (page 4, lines 27-28 and page 33, line 31 to page 34, line 1). Melmed et al teach transgenic non-human animals that are capable of expressing exogenous PTTG polypeptide or the inactivated mutated form of the PTTG peptide, such as the well-known knock-out transgenics (page 18, lines 16-25). Melmed et al teach that homologous recombinant techniques allow for the replacement of the endogenous gene with a recombinant or mutated gene resulting in altered expression of the PTTG polypeptide (page 19, lines 5-12). Melmed et al teach that transgenic animal model systems are useful for in vivo screening of compounds for identification of specific ligands which activate or inhibit protein responses (page 19, lines 18-20) and that in vivo screening assays provide modulators, agonists or antagonists of the invention polypeptides (page 19, lines 32-34). Melmed et al teach a bioassay in which the PTTG polypeptide are contacted with an unknown test substance (page 19, line 35 to page 20, line 5). Melmed et al teach that typical "control" cells for the methods of identifying compounds that modulate PTTG activity are a "control" cell that is identical to the transfected cells with the exception that said control cell does not express the native PTTG protein (page 20, lines 29-32). Melmed et al do not specifically teach that the cells are isogenic cell, wherein the cell not expressing the wild-type protein is expressing the defective protein.

Lengauer et al teach that chromosomal instability is a major factor in the vast majority of cancers and that this is observed as aneuploidy (page 643, first column, under Alterations in chromosome number). Lengauer et al teach that colorectal cells exhibit chromosomal instability (page 645, second column, under heading Relationship between MIN and CIN and page 646, second column, second paragraph). Lengauer et al teach that in order to test if a specific gene is responsible for chromosomal instability it is necessary to have in hand an immortalized cell line in which the targeted gene has been deleted (page 647, second column, lines 4-18). Lengauer et al further teach that the chromosomal instability of cancer cells may provide a valid therapeutic target and can be expected to be sensitive to particular chemical agents relative to the same cells not exhibiting chromosomal instability (page 648, second column).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to make a homozygous PTTG-defective mammalian cell line and to

use said cell line in combination with an isogenic cell line for the screening of compounds to identify agents which preferentially inhibit or kill the homozygous PTTG-defective cell line in contrast to the isogenic non-defective cell line. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Melmed et al on assays of test compounds on cell expressing PTTG, and control cells witch differ from the test cells with respect to the non-expression of native PTTG; PTTG defective cell lines, the inhibition of cell proliferation by the transfection of wild-type PTTG and homologous recombination to make a cell line which does not express its endogenous gene; and the teachings of Lengauer et al on necessity of having immortalized cell lines in which the gene purported to be responsible for chromosomal instability is deleted and on the validity of targeting the cells exhibiting chromosomal instability as potential therapeutic targets for particular chemical agents. Further, although Lengauer et al do not specifically teach a pair of isogenic cell lines in which the first cell line is homozygous PTTG defective and a second cell line which is PTTG-proficient, Lengauer et al do teach a rigorous criteria necessary for the determination of a gene which would be involved in chromosomal instability due to the number of genes which may be involved in the occurrence of aneuploidy. Therefore, one of skill in the art would use isogenic cell lines in order to minimize any differences between the homozygous PTTG defective cell line and the PTTG proficient cell line.

6. Claims 10, 16-18 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Melmed et al and Morales et al and Lengauer et al as applied to claims 10, 16, 18 and 23 above, and further in view of Fiebig et al (Human Tumor Zenografts, In: anticancer Drug Development, 1988, cited in a previous Office action).

Claim 17 embodies the method of claim 10 wherein the cell lines are in xenografts when contacted with the test compounds.

Fiebig et al teach methods of testing anti-cancer drugs using cell lines in xenografts. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to test the homozygous PTTG-defective cell line and the isogenic wild-type PTTG -proficient cell line in xenografts. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Fiebig et al on

the nexus between the ability of a drug to kill or inhibit tumor cells when transplanted in a xenograft and the ability of the drug to kill or inhibit tumor cells in patients.

7. All other rejections and objections as stated or maintained in the previous Office action are withdrawn.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
8/22/2005

Karen A. Canella
KAREN A. CANELLA PH.D
PRIMARY EXAMINER